Information Disclosure Statement

The Action states that the AG reference WO 95/06211 in the Information Disclosure Statement filed August 24, 2002 has not been considered because it is not in English. Applicants herein submit the above PCT application in English, along with a PTO-1449 form. Consideration of this reference is respectfully requested.

Rejection under 35 U.S.C. § 102(b)

Claims 2 and 5 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Bult *et al.* (Science 273: 1058-1073, 1996) as evidenced by Kohara (GenBank Acc. No. D64402, 1995). More specifically, the Action asserts that Bult *et al.* teach a 47mer protein that comprises the sequence IYSYX (citing the entire article of Bult *et al.*) and thus comprises at least 5 consecutive amino acids of SEQ ID NO:1, based on nucleotide sequence of the prokaryotic organism *Methanococcus jannaschii*. In addition, the Action asserts that the above sequence is transcribed in at least another eukaryotic organism as evidenced by Kohara's GenBank submission.

Applicants respectfully traverse this ground of rejection. Applicants' review of the Bult *et al.* reference fails to identify any description of a 47mer protein that comprises the sequence IYSYX. In addition, the translations of the mRNA disclosed by Kohara in three possible reading frames fail to identify a four amino acid fragment that has the sequence IYSY. Should this ground of rejection be maintained, Applicants respectfully request that the Examiner point out the specific portion of section of the Bult *et al.* reference that recites the 47mer protein containing IYSYX and provide the explanation as to how the mRNA disclosed by Kohara is translated into a polypeptide that contains the sequence IYSY.

Accordingly, Applicants submit that this ground of rejection has been overcome. Withdrawal of the rejection under 35 U.S.C. § 102(b) is respectfully requested.

Rejection under 35 U.S.C. § 112, First Paragraph (Enablement)

Claims 2-6, 27-32 and 35-37 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly containing subject matter not adequately described in the specification. More specifically, the Action asserts that (1) the specification is not enabling for the current claim

scope because it does not disclose the sequence identity of cell adhesion recognition (CAR)-containing peptides that actually reduce cell adhesion in the disclosed example, nor the 9 amino acid CAR sequence used to make the antibodies that have cell adhesion modulating activity as disclosed in Examples 2 and 4; (2) there is no clear guidance from the specification as to the minimum number of amino acids from the deduced consensus amino acid sequence for a claudin CAR sequence (SEQ ID NO:1) that is necessary to modulate claudin-mediated processes, such as cell adhesion; and (3) there is no clear guidance from the specification as to what effect cyclization of a claudin CAR sequence will have on its cell adhesion functions.

Applicants respectfully traverse this ground of rejection. As an initial matter, it is noted that the Patent Office has an initial burden to establish a *prima facie* case of non-enablement by providing sufficient supports for doubting the objective truth of the statements in an application. Staehelin v. Secher 24 USPQ2d 1513, 1516 (B.P.A.I. 1992). In addition, an Applicant is *not* required to specifically exemplify all embodiments of an invention. The requirements of 35 U.S.C. § 112, first paragraph, can be fulfilled by the use of *illustrative* examples or *broad* terminology. *In re* Anderson, 176 U.S.P.Q. 331 (CCPA 1973).

With respect to the Examiner's skepticism regarding the capability of an agent comprising SEQ ID NO:1 of modulating claudin-mediated process, Applicants herewith submit a Declaration under 37 C.F.R. § 1.132 to present data showing that a peptide comprising SEQ ID NO:1 is capable of inhibiting the formation of tight junctions in epithelial cells.

As to the assertion related to the minimum number of amino acids of SEQ ID NO:1 required for modulating claudin-mediated processes, Applicants submit that there is no sufficient evidentiary support in the Action for doubting that the claimed modulating agent that comprises at least five, seven or eight amino acids of a claudin CAR sequence having the formula of SEQ ID NO:1 is capable of modulating cell adhesion. Peptides containing as few as three amino acid portions of proteins involved in cell adhesion are known to have cell adhesion modulating activities. For instance, a cyclic peptide containing only the HAV tripeptide motif of cadherin was shown to possess an inhibitory effect on cell adhesion (*see, e.g.*, U.S. Pat. No. 6,6031, 072). Likewise, in integrins, the RGD tripeptide has similar effects as longer peptides in inhibiting integrin-matrix interactions (*see, e.g.*, Ali *et al.*, J. Med. Chem. 37: 769-80, 1994, which is attached for the Examiner's convenience). Thus, the fact that the above claims recite

small numbers of amino acid residues of a claudin CAR sequence does not by itself provide sufficient countervailing evidence for doubting the capability of the claimed agent of modulating cell adhesion.

In addition, to facilitate allowance and without acquiescing to the above assertions in the Action, Applications have amended claims 2-4 to recite that Aaa, Baa and Caa of SEQ ID NO:1 indicate amino acid residues present in a naturally occurring claudin. Thus, although Aaa, Baa and Caa of SEQ ID NO:1 derived from one claudin molecule may be different from the amino acid residues at their corresponding positions of SEQ ID NO:1 derived from another claudin, they cannot be randomly assigned, but must be dictated by the sequences of the naturally occurring claudin molecules from which they are derived. Accordingly, the cell adhesion modulating agent recited in the currently pending claims does not have as many sequence variations as speculated in the Action.

As to the assertion in the Action regarding the effect of cyclization of a claudin CAR sequence on its cell adhesion functions, Applicants submit that there is no sufficient support for doubting the cell adhesion modulating capability of a cyclic peptide that comprises five or more amino acid residues of a claudin CAR sequence having the formula of SEQ ID NO:1. It has been known that both cyclic and linear peptides that comprises a cadherin CAR sequence are capable of modulating cell adhesion (*see, e.g.*, U.S. Pat. Nos. 6,031,072; 6,277,824). In addition, for a given cyclic peptide that comprises a cadherin CAR or a portion thereof, one of ordinary skill in the art may use the methods disclosed in the application to verify or evaluate its cell adhesion modulating activities (*see, e.g.*, page 39, line 26 to page 45, line 11 of the present application). Accordingly, Applicants submit that in view of the teaching in this application, a skilled artisan is able to make and use the claimed cyclic peptides as cell adhesion modulating agents.

In view of the above remarks, Applicants submit that this ground of rejection has been overcome. Withdrawal of this rejection under 35 U.S.C. § 112, first paragraph, is respectfully requested.

Rejection under 35 U.S.C. § 112, First Paragraph (Written Description)

Claims 2-6, 27-32 and 35-37 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter not adequately described in the specification. More specifically, the Action notes that SEQ ID NO:1 is an 8mer in which 3 residues can be, with one exception, any amino acid. The Action asserts that it is unclear which amino acids can be included in the group of "independently selected" amino acids and still comprise a claudin CAR sequence, and that it is unclear from the disclosure whether the independently selected amino acids must be present in equivalent positions as one of the sequences used to derive the claudin CAR consensus.

As discussed above, to facilitate allowance and without acquiescing to the above assertions in the Action, Applications have amended claims 2-4 to recite that Aaa, Baa and Caa of SEQ ID NO:1 indicate amino acid residues present in a naturally occurring claudin. Thus, the identities of the above three amino acids in SEQ ID NO:1 are dictated by naturally occurring claudin sequences and cannot be randomly assigned. Applicants submit that in view of the above amendment, one of ordinary skill in the art would know that these three amino acids are present in equivalent positions as one of the sequences used to derive the claudin CAR consensus.

Rejection under 35 U.S.C. § 112, First Paragraph (New Matter)

Claims 2-6, 27-32 and 35-37 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing new matter. More specifically, the Action asserts that there is no support in the specification or claims as originally filed for the recitation "wherein Aaa is not glycine when Lys/Arg is Arginine and Baa is aspartic acid."

While disagreeing with the characterization of the above phase as new matter, Applicants have eliminated the recitation of this phase because this phrase becomes unnecessary in view of the amendment to claims 2-4 related to the three amino acid residues Aaa, Baa and Caa of SEQ ID NO:1. This phrase was originally added to distinguish the claimed cell adhesion modulating agent from the peptide CRGDSFVGC disclosed by Ruoslahti *et al.* (U.S. Pat. No. 5,981,478). However, because the peptide CRGDSFVGC or portions thereof that comprise at least 5 amino acids are not present in naturally occurring claudins, this peptide does not anticipate the modulating agent of the currently pending claims.

In view of the above remarks, Applicants submit that the rejection under 35 U.S.C. § 112, first paragraph, has been overcome. Withdrawal of this rejection is respectfully requested.

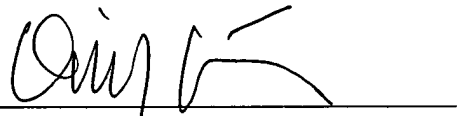
Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version With Markings to Show Changes Made.**" Also enclosed is a copy of Limited Recognition Under 37 CFR § 10.9(b).

On the basis of the above amendments and remarks, reconsideration of the application and its allowance are respectfully requested. Should the Examiner have any additional questions, she is respectfully encouraged to contact the undersigned attorney at (206) 622-4900.

Respectfully submitted,

Orest Blaschuk et al.

SEED Intellectual Property Law Group PLLC



Qing Lin, Ph.D.
(See Limited Recognition)

QXL:jab

Enclosures:

Version With Markings to Show Changes Made
Copy of Limited Recognition Under 37 CFR § 10.9(b)
Declaration Under 37 CFR § 1.132
PTO-1449, 1 IDS reference (Ali *et al.*, J. Med. Chem. 37:769-80, 1994)

701 Fifth Avenue, Suite 6300
Seattle, Washington 98104-7092
Phone: (206) 622-4900
Fax: (206) 682-6031

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claims 2-4 have been amended as follows:.

2. (Four Times Amended) A cell adhesion modulating agent that:

(a) comprises at least five consecutive amino acid residues of ~~a claudin CAR sequence having~~ the formula:

Trp-Lys/Arg-Aaa-Baa-Ser/Ala-Tyr/Phe-Caa-Gly (SEQ ID NO:1)

wherein Aaa, Baa and Caa indicate ~~independently selected~~ amino acid residues that are present in a naturally occurring claudin; Lys/Arg is an amino acid that is lysine or arginine; Ser/Ala is an amino acid that is serine or alanine; and Tyr/Phe is an amino acid that is tyrosine or phenylalanine~~, wherein Aaa is not glycine when Lys/Arg is arginine and Baa is aspartic acid~~; and

(b) contains no more than 50 consecutive amino acid residues present within the claudin.

3. (Four Times Amended) A cell adhesion modulating agent that:

(a) comprises at least seven consecutive amino acid residues of ~~a claudin CAR sequence having~~ the formula:

Trp-Lys/Arg-Aaa-Baa-Ser/Ala-Tyr/Phe-Caa-Gly (SEQ ID NO:1)

wherein Aaa, Baa and Caa indicate ~~independently selected~~ amino acid residues that are present in a naturally occurring claudin; Lys/Arg is an amino acid that is lysine or arginine; Ser/Ala is an amino acid that is serine or alanine; and Tyr/Phe is an amino acid that is tyrosine or phenylalanine~~, wherein Aaa is not glycine when Lys/Arg is arginine and Baa is aspartic acid~~; and

(b) contains no more than 50 consecutive amino acid residues present within the claudin.

4. (Twice Amended) A cell adhesion modulating agent that:

(a) comprises at least eight consecutive amino acid residues of ~~a claudin CAR sequence having~~ the formula:

Trp-Lys/Arg-Aaa-Baa-Ser/Ala-Tyr/Phe-Caa-Gly (SEQ ID NO:1)

wherein Aaa, Baa and Caa indicate ~~independently selected~~ amino acid residues that are present in a naturally occurring claudin; Lys/Arg is an amino acid that is lysine or arginine; Ser/Ala is an amino acid that is serine or alanine; and Tyr/Phe is an amino acid that is tyrosine or phenylalanine; and

(b) contains no more than 50 consecutive amino acid residues present within the claudin.

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